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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/635,864	08/10/2000	Jeffrey M. Friedman	600-1-087CIP1	6312

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EXAMINER	
SAOUD, CHRISTINE J	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/635,864	FRIEDMAN ET AL.	
	Examiner	Art Unit	
	Christine J. Saoud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61-67 and 69-88* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61-67 and 69-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *22 May 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 22 May 2006 has been entered.

Claims 61-67 and 69-74 have been amended in the amendment filed 22 May 2006. Claims 1-60 and 68 have been canceled. Claims 61-67 and 69-88 are pending and under examination in the instant Office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Applicant's arguments filed 22 May 2006 have been fully considered but they are not deemed to be persuasive.

Information Disclosure Statement

The information disclosure statement filed 22 May 2006 fail to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the

Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; ***(3) the application number of the application in which the information disclosure statement is being submitted on each page of the list***; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement.

Applicant has provided copies of information disclosure statements which were filed in the parent applications. These copies of the PTO-892 forms do not appear to be a proper submission according to 37 CFR 1.98(a)(1). Applicant did not include the correct application number, filing date, art unit, and examiner name on each page of the list. Applicant is not required to include the art unit and examiner name, but if it is included, it should be accurate. It is requested that in future submissions, care is taken to comply with 37 CFR 1.98(a)(1).

Claim Rejections - 35 USC § 112

Claim 63 (and dependent claims 69-88) stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant states that the specification provides an alignment of the human and mouse protein in Figure 4 and demonstrates that 83% of the amino acids are

identical between the two proteins. Applicant argues at page 9 of the response that these molecules are exemplary and the specification "sets out adequate teaching to the skilled artisan for making and testing additional such polypeptides with 83% or greater amino acid identity". Applicant's arguments have been fully considered but are not persuasive. The ability to make a protein and test for activity to see if it meets the limitations of the claims is not a written description of the molecules. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The specific molecular structure is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. What is being claimed is a genus of molecules which were never described in the instant specification. In fact, the single data point of 83% sequence identity does not support the genus claim to any protein having 83% or greater amino acid sequence identity to either the mouse or human sequence. This would encompass as much as 17% variability from the human and 17% variability from the mouse, and therefore 34% variability between different molecules. The single disclosure of 83% is not a basis for the broad claim of the range 83% or greater amino acid sequence identity in the instant specification as originally filed.

Applicant argues that a similar claim was allowed in a corresponding application. Applicant is reminded that each application is examined on its own merits. Furthermore, the Examiner is not permitted to comment on the claims issued in the corresponding application – a patent is presumed valid (35 U.S.C.

282). It is noted that the patent to which Applicant is referring (5,935,810) issued in November, 1999. In December of 1999, the USPTO issued "Revised Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, first paragraph" and these guidelines were finalized in January of 2001 (see Federal Register, Vol. 64, No. 244 and Federal Register, Vol. 66, No. 4). The instant claims were examined in light of these guidelines.

Applicant asserts that the presence of a number of "homologous" sequences were identified using hybridization techniques. However, there is no disclosure as to the structure of these nucleic acids or the encoded proteins, so there is no disclosure that any of the encoded proteins were at least 83% identical.

Vas-Cath In. v. Mahurkar, 19 USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for the purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present is a functional recitation of modulating body weight. There is no structure recited, except that the protein should be about 145 amino

acids long. The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Claims 61-67 and 69-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule that encodes an OB-polyaminoacid polymer fusion protein, does not reasonably provide enablement for a nucleic acid molecule that encodes an OB polypeptide and also encodes one or more polyaminoacid polymers ***attached*** to said OB polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

It is clear that Applicant would like to claim a nucleic acid molecule that encodes a fusion protein of OB polypeptide and a polyaminoacid polymer. However, the claims recite the limitation that the polymers are "attached" to the OB polypeptide. Attachment could occur through a number of different types of bonds, and at a number of different amino acid positions. A nucleic acid molecule would not be able to encode for a branched molecule or for an attachment that is other than a peptide bond. If the specification contains support for the term "fused", this possibly could obviate this ground of rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 61-67 and 69-88 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims include the limitation of "said nucleic acid optionally in a pharmaceutical carrier" (see claims 61-67, for example). However, the claims are also directed to "An isolated nucleic acid". This appears to place some ambiguity on whether the claims are a composition or not. It is suggested that this language be removed from the claims and additional dependent claims directed to a composition comprising the nucleic acid and a pharmaceutically acceptable carrier be added.

Claims 77-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an ***isolated or cultured*** cell comprising an expression vector, does not reasonably provide enablement for a host cell comprising an expression vector. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Examiner has interpreted the claims as reading on isolated host cells, as well as host cells in the context of a multicellular, transgenic organism and host cells intended for gene therapy. The specification of the instant application teaches that OB gene products can be expressed in cells and the cells can be

transplanted in a subject (see page 64, paragraph 2) as well as the OB gene being introduced into human fat cells for gene therapy (see page 65, first full paragraph). However, there are no methods or working examples disclosed in the instant application whereby cells were transplanted in a subject and the cells were demonstrated to express the OB polypeptide or where gene therapy was performed on a human. The unpredictability of the art is *very high* with regards to making transgenic animals. For example, Wang et al. (Nuc. Acids Res. 27: 4609-4618, 1999; pg 4617) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the original gene. Likewise, Kaufman et al (Blood 94: 3178-3184, 1999) found transgene expression levels in their transfected animals varied from "full" (9 %) to "intermediate" to "none" due to factors such as "vector poisoning" and spontaneous structural rearrangements (pg 3180, col 1, 2nd full paragraph; pg 3182-3183).

With regard to transplantation of cells expressing the OB polypeptide, the specification does not teach any methods or working examples that indicate a OB nucleic acid is introduced and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of vector would introduce the OB nucleic acid into the cell or in what quantity and duration. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and

although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A., J Pharm Pharmacology 53: 1169-1174, 2001; abstract). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express an OB nucleic acid into the cell of an organism. Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express an OB nucleic acid in the cell of an organism or be able to produce an OB protein in that cell.

Due to the large quantity of experimentation necessary to generate a transgenic animal expressing the OB protein and to introduce and express an OB nucleic acid in a cell of an organism for therapy, the lack of direction/guidance presented in the specification regarding how to introduce an OB nucleic acid in the cell of an organism to be able produce that OB polypeptide, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of making transgenic animals and the unpredictability of transferring genes into an organism's cells,

and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. (Please note that this issue could be overcome by amending the claims to recite, for example, "An isolated host cell...").

Double Patenting

Claims 61-67, 69-88 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 5,935,810 and claims 1-21 of U.S. Patent No. 6,309,853 for the reasons of record in the previous Office actions.

Applicant has pointed out the typographical error in the patent number (810 instead of 801). The correction has been made.

U.S. Pat. No. 5,935,810 and 6,309,853 claim nucleic acids encoding OB polypeptides, which are the same as the OB polypeptides recited in the instant claims. However, some of the instant claims do include a recitation of "having one or more polymers attached thereto" and "optionally in a pharmaceutical carrier". As pointed out before, it is not clear if these limitations are to be placed on the protein or the nucleic acid. Regardless, the proteins of '810 and '853 use comprising language and therefore, conceivably include additional amino acids, such as polyamino acids. Therefore, the instant claims are not identical to those of '810 and '853, but they are encompassed by the claims of '810 and '853.

This is a provisional obviousness-type double patenting rejection.

Applicant argues that the claims are distinct from the issued patents because the instant claims are directed to nucleic acids which encode both OB polypeptide(s) and also one or more polymers attached to the polypeptides. Applicant's arguments have been fully considered, but are not persuasive. The claims in the issued patents include comprising language, so the nucleic acid could encode a protein having an amino acid sequence and also encode additional amino acids. The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as indicated above. Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent.

Claims 61-67, 69-88 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 5,935,810 and claims 1-21 of U.S. Patent No. 6,309,853 for the reasons of record in the previous Office actions and further in view of Davis et al. (U.S. Pat. No. 4,179,337) and Stahl et al. (U.S. Pat. No. 5,470,843).

Applicant argues that the claims are distinct from the issued patents because the instant claims are directed to nucleic acids which encode both OB polypeptide(s) and also one or more polymers attached to the polypeptides. However, polypeptides having one or more polymers attached to the polypeptides is old and well known in the art. Davis et al. teach that coupling of

biologically active polypeptides to polymers is beneficial to increase the stability and circulation time of the polypeptide as well as decreasing immunogenicity (see columns 1-2). Stahl et al. teach that polymers which are suitable for *in vivo* use include polyaminoacids (see column 7, lines 4-13). Therefore, it would have been *prima facie* obvious to attach a polymer, specifically a polyaminoacid, to the leptin (OB) molecule of the '810 or '853 patent for the advantage of increased stability and circulation time as well as for decreased immunogenicity. Additionally, because polyaminoacids can be encoded by a nucleic acid, it also would have been *prima facie* obvious to make such molecules using a nucleic acid that encoded a fusion protein of leptin (OB) and the polyaminoacid polymer because this would eliminate the additional step of coupling the polyaminoacid polymer to the protein of interest. One would have a reasonable expectation of success in generating such a molecule because generation of fusion proteins was routine in the art at the time of the instant invention, as was use of polymers with biologically active proteins as evidenced by Davis et al. Therefore, the invention as a whole would have been *prima facie* obvious at the time it was made, absent evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud whose telephone number

is 571-272-0891. The examiner can normally be reached on Monday-Friday, 6AM-2PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CHRISTINE J. SAOUD
PRIMARY EXAMINER